(FILE 'HCAPLUS' ENTERED AT 11:45:47 ON 05 FEB 2003)

L1 9691 SEA FILE=HCAPLUS ABB=ON PLU=ON INCUBAT? AND LYMPHOCYTE

L8 103 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 AND TOXIC?(5A)EFFECT?

L9 11 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND (AMELIORAT? OR REVERS?)

L16 4232 SEA FILE=HCAPLUS ABB=ON PLU=ON TOXIC?(S)(AMELIORAT? OR REVERS?)

L18 143 SEA FILE=HCAPLUS ABB=ON PLU=ON L16 AND LYMPHOCYT?

L19 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L18 AND INCUBAT?

L20 14 L9 OR L19

L20 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:188851 HCAPLUS

TITLE: Brief triphenyltin exposure causes irreversible inhibition of the cytotoxic function of human natural killer cells

AUTHOR(S): Wilson, Sharnise; Loganathan, Bommanna G.; Whalen, Margaret M.

CORPORATE SOURCE: Department of Chemistry, Tennessee State University, Nashville, TN, 37209, USA

SOURCE: Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002 (2002), ENVR-166. American Chemical Society: Washington, D. C.
CODEN: 69CKQP

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Phenyltin (PT) contamination has been reported in water, sediment, and fish. Triphenyltin (TPT) has been implicated in a wide spectrum of **toxic effects** in exposed animals, including increased tumor formation. Human exposure to TPT might come from occupational exposure as well as consumption of contaminated food. Natural Killer cells are a primary immune defense against tumor and virally infected cells. Previously, we reported that exposure to TPT significantly inhibited the tumor killing capacity of human NK cells. In this study we examine whether the inhibition of NK-cell cytotoxicity induced by a 1 h exposure to TPT is **reversible**, when the cells are allowed to recover in TPT-free media for up to 6 days. The results revealed that exposure to 750 nM TPT for 1h caused a 57% decrease in NK-cytotoxic function. However, if the cells were allowed to **incubate** in TBT-free media for 24 h there was an 84% inhibition of NK cytotoxicity. There was no significant recovery of NK-cytotoxic function when the **lymphocytes** were allowed to **incubate** in TPT-free media for up to 6 days. The results indicated that short-term exposure to TPT caused persistent neg. effects on NK-cell ability to kill cancer cells.

L20 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1991:484877 HCAPLUS

DOCUMENT NUMBER: 115:84877
TITLE: Studies on the **reversal** of azidothymidine **toxicity** in human **lymphocytes** by cytidine and uridine
AUTHOR(S): Cox, S.
CORPORATE SOURCE: Dep. Virol., Kaolinska Inst., Stockholm, S-105 21, Swed.
SOURCE: Antiviral Chemistry & Chemotherapy (1991), 2(1), 23-8
CODEN: ACCHEH; ISSN: 0956-3202
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **toxicity** of 3'-azidothymidine (AZT) in human **lymphocytes** has been shown previously to be **reversed** by co-**incubation** with the ribonucleosides cytidine or uridine. In the present paper, the effects of 3'-azidothymidine and cytidine/uridine, both alone and in combination, were studied upon key processes in **lymphocytes** in order to discover more about the mechanism of **toxicity reversal**. In these expts. 3'-azidothymidine had only minor effects on the ribonucleoside triphosphate pools. Cytidine increased the CTP pool, and uridine the UTP pool. Co-**incubation** with AZT caused similar changes to **incubation** with cytidine or uridine alone. **Toxicity reversal** was not linked to replacement of deficient ribonucleoside triphosphate pools. 3'-Azidothymidine caused the excretion of thymidine from **lymphocytes**. **Incubation** with cytidine and uridine increased the intracellular cytidine and uridine pools, resp. Co-**incubation** with 3'-azidothymidine increased still further the intracellular cytidine and uridine pools. Cytidine and uridine did not affect the intracellular 3'-azidothymidine pool. The toxicity of 3'-azidothymidine was increased by co-**incubation** with the bases adenine, guanine, hypoxanthosine, and uracil, but not by dihydrouracil, thymine, or xanthine.

IT **Lymphocyte**
(azidothymidine **toxicity** to, ribonucleoside **reversal** of, mechanism of)

IT Nucleosides, biological studies
RL: BIOL (Biological study)
(in **lymphocytes**, azidothymidine **effect** on, **toxicity** in relation to)

IT 65-71-4, Thymine 66-22-8, Uracil, biological studies 68-94-0, Hypoxanthine 69-89-6, Xanthine 73-24-5, Adenine, biological studies 73-40-5, Guanine 146-80-5, Xanthosine 504-07-4, Dihydrouracil
RL: BIOL (Biological study)
(azidothymidine **lymphocyte** toxicity response to)

IT 58-96-8, Uridine 65-46-3, Cytidine
RL: BIOL (Biological study)
(azidothymidine **lymphocyte toxicity reversal** by, mechanism of)

IT 50-89-5, Thymidine, biological studies
RL: BIOL (Biological study)
(excretion of, by **lymphocytes**, azidothymidine stimulation of, toxicity in relation to)

IT 56-65-5, 5'-ATP, biological studies 63-39-8, Uridinetriphosphate 65-47-4, Cytidine 5'-(tetrahydrogen triphosphate) 86-01-1, Guanosinetriphosphate

RL: BIOL (Biological study)
(in **lymphocyte**, azidothymidine effect on)
IT 30516-87-1, 3'-Azidothymidine
RL: BIOL (Biological study)
(**lymphocyte toxicity** of, ribonucleoside **reversal** of)

L20 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:476411 HCAPLUS
DOCUMENT NUMBER: 113:76411
TITLE: Influenza peptide-induced self-lysis and down-regulation of cloned cytotoxic T cells
AUTHOR(S): Pemberton, R. M.; Wraith, D. C.; Askonas, B. A.
CORPORATE SOURCE: Natl. Inst. Med. Res., London, UK
SOURCE: Immunology (1990), 70(2), 223-9
CODEN: IMMUAM; ISSN: 0019-2805
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Virus-specific cytotoxic T-cell (Tc) clones can lyse target cells in vitro in the presence of their specific peptide epitopes. The lytic potency of murine influenza nucleoprotein (NP)-specific Tc clones was investigated after observing that target cell killing was reduced in the presence of high (>0.2 .mu.M) concns. of specific NP peptide antigen. Following **incubation** of Tc for 16 h in the presence of a range of peptide concns., two effects were obsd.; (i) a peptide dose-dependent mortality of Tc, which has been attributed to self-lysis by clonal Tc in the presence of specific peptide; (ii) and a reduced ability to specifically lyse NP-expressing target cells whilst retaining lectin-dependent lytic activity in the surviving Tc. This functional down-regulation was **reversible** after 24 h **incubation** in the absence of peptide. **Toxic effects** were excluded, since inhibition of specific target lysis by Tc was mediated only be pretreatment with specifically recognized peptide.
IT Nucleoproteins
RL: BIOL (Biological study)
(of influenza virus, peptide of, cytotoxic T cells self lysis and down regulation induction by)
IT Peptides, biological studies
RL: BIOL (Biological study)
(of nucleoprotein, of influenza virus, cytotoxic T cells self lysis and down regulation induction by)
IT Cytolysis
(self, of cytotoxic T cells, influenza peptide induction of)
IT **Lymphocyte**
(T-, cytotoxic, influenza peptide induction of self lysis and down-regulation of)
IT Virus, animal
(influenza, peptide of nucleoprotein of, cytotoxic T cells self lysis and down regulation induction by)

L20 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:419059 HCAPLUS
DOCUMENT NUMBER: 113:19059
TITLE: Inability of poly-ADP-ribosylation inhibitors to protect peripheral blood **lymphocytes** from the **toxic effects** of ADA inhibition

AUTHOR(S): Ganeshaguru, K.; Piga, A.; Latini, L.; Hoffbrand, A. V.
CORPORATE SOURCE: Sch. Med., R. Free Hosp., London, UK
SOURCE: Advances in Experimental Medicine and Biology (1989), 253B(Purine Pyrimidine Metab. Man 6, Pt. B), 251-8
CODEN: AEMBAP; ISSN: 0065-2598
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effectiveness of two inhibitors of poly-ADP-ribosylation, nicotinamide and 3-aminobenzamide, as rescue agents in resting and PHA-stimulated **lymphocytes** damaged by the combination of deoxycoformycin (dCF) plus deoxyadenosine (dAdo) was evaluated. **Incubation** with dCF (10-5M) and dAdo (10-4M) for 18 h, inhibited protein and RNA synthesis in unstimulated **lymphocytes** and impaired the ability of the cells to methylcellulose. Predominantly dead cells using trypan blue exclusion were obsd. at day 4, in both unstimulated and PHA-stimulated **lymphocytes**, whether or not the drugs were removed at 18 h. The no. of viable cells at day 4 increased from 13.7% to 41.1% with the addn. of 5 mM nicotinamide, and to 28.8% with 5 mM 3-aminobenzamide added with dCF and dAdo. Although nicotinamide was able to prevent a fall in NAD concn. for 24 h (but not for 48 h) and to reduce the fall of cell ATP concn., the inhibition by dCF and dAdo of protein synthesis, RNA synthesis, ability of cells to form colonies or to respond to PHA was not **reversed**. Apparently, inhibition of NAD utilization by inhibiting ADP-ribosylation with nicotinamide or 3-aminobenzamide does not protect cells in vitro from deoxyadenosine toxicity with adenosine deaminase (ADA) inhibition and is not likely to give significant clin. benefit in ADA deficiency.

IT Protein formation
Ribonucleic acid formation
Deoxyribonucleic acids
RL: BIOL (Biological study)
(deoxyadenosine and deoxycoformycin effect on, in human **lymphocyte**, aminobenzamide and nicotinamide effect on, adenosine deaminase in relation to)

IT **Lymphocyte**
(deoxyadenosine and deoxycoformycin **toxicity** to human, aminobenzamide and nicotinamide **effect** on, adenosine deaminase in relation to)

IT 53-84-9, NAD 56-65-5, 5'-ATP, biological studies
RL: BIOL (Biological study)
(deoxyadenosine and deoxycoformycin effect on, in human **lymphocyte**, aminobenzamide and nicotinamide effect on, adenosine deaminase in relation to)

IT 9026-93-1, Adenosine deaminase
RL: BIOL (Biological study)
(deoxyadenosine and deoxycoformycin toxicity to **lymphocytes** in relation to)

IT 98-92-0, Nicotinamide 3544-24-9, 3-Aminobenzamide
RL: BIOL (Biological study)
(deoxyadenosine and deoxycoformycin toxicity to **lymphocytes** response to, adenosine deaminase in relation to)

IT 958-09-8, Deoxyadenosine 53910-25-1, Deoxycoformycin
RL: ADV (Adverse effect, including toxicity); BIOL (Biological

cell activity
AUTHOR(S): Gherman, Maria; Herberman, Ronald B.; Sulica, Andrei
CORPORATE SOURCE: Dep. Immunol., Babes Inst., Bucharest, Rom.
SOURCE: Natural Immunity and Cell Growth Regulation (1989), 8(5), 255-65
CODEN: NICRDR; ISSN: 0254-7600
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Monomeric IgG (mIgG) was previously shown to inhibit human natural killer (NK) cell activity when effector cells were treated prior to the cytotoxic assay. In the present study the interaction between neg. regulation by mIgG and pos. regulation by interleukin-2 (IL-2) was examd. Although a dose-dependent boosting of NK activity was found upon **incubation** of nonadherent **lymphocytes** (NAL) with recombinant or natural IL-2 for 2 h at 37.degree., the NK effector cells remained responsive to down-regulation to mIgG. However, when NAL were treated with IL-2 under supraoptimal conditions (higher doses and longer periods of **incubation** than required for optimal boosting of NK activity) the subsequent addn. of mIgG had a reduced inhibitory effect. This partial resistance to suppression by inhibitory IgG was obsd. only when the second treatment was performed without washing the IL-2-pretreated effector cells. , Addn. of antihuman interferon .gamma. antibodies during the **incubation** of NAL with IL-2 almost abolished the loss of responsiveness of the IL-2-activated killer cells to mIgG-induced inhibition. Thus, interferon .gamma. can **reverse** or block the down-regulation of NK activity by mIgG.

IT Neoplasm, toxic chemical and physical damage
(lymphokine-activated killer cells **toxicity** for, monomeric IgG **effect** on)

IT Immunoglobulins
RL: BIOL (Biological study)
(G, natural killer cell inhibition by monomeric, interleukin 2 **reversal** of, antitumor activity in relation to, of humans)

IT Lymphokines and Cytokines
RL: BIOL (Biological study)
(interleukin 2, monomeric IgG-induced inhibition of human natural killer cells **reversal** by)

IT **Lymphocyte**
(natural killer, monomeric IgG-induced inhibition of human, interleukin 2 **reversal** of, antitumor activity in relation to)

IT Interferons
RL: BIOL (Biological study)
(.gamma., interleukin 2 **reversal** of monomeric IgG-induced inhibition of human natural killer cells response to)

L20 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:509033 HCAPLUS
DOCUMENT NUMBER: 111:109033
TITLE: Crystal polymorphs of xanthosine, a method for their preparation, and their use as immunomodulators
INVENTOR(S): Gordon, Paul
PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8808847	A2	19881117	WO 1988-US1467	19880510
WO 8808847	A3	19891102		
W: AT, AU, BB, BG, BR, CH, DE, DK, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU				
RW: AT, BE, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
AU 8821339	A1	19881206	AU 1988-21339	19880510
CN 1031537	A	19890308	CN 1988-103908	19880512
ES 2009277	A6	19890916	ES 1988-1523	19880516

PRIORITY APPLN. INFO.: US 1987-50818 19870515
US 1987-54376 19870526
WO 1988-US1467 19880510

AB A method for prepg. a crystal polymorph of a xanthosine salt comprises adding xanthosine to a solvent, adding an equimolar amt. of strong base, heating the mixt. at a predetd. rate to a temp. sufficient to dissolve the xanthosine and to overcome energy barriers which prevent the conversion of xanthosine to other polymorphic configurations; xanthosine is then pptd., the mixt. is cooled, and lyophilized to give cryst. polymorphous xanthosine. A mixt. contg. 0.4 mol xanthosine-2H2O, 0.4 mol choline, and MeOH to 110 mL was heated from room temp. to 80.degree. in 20 min; at 75-80.degree. abrupt crystn. occurred and the resulting choline xanthosinate (I) was lyophilized; this product was nonhygroscopic. Nonhygroscopic Na xanthosinate was prepd. from a soln. contg. 0.4 mol xanthosine-2H2O, 0.4 mol NaOH, and 160 mL H2O, and adding 200 mL MeOH. I had cryst. properties, whereas Na xanthosinate and xanthosine-2H2O were amorphous. I exhibited a small degree of hydrolyis in aq. soln. (i.e. ion pairing) and the pH of aq. I solns. was neutral (pH 7.5); this property permits their use in vivo. Peripheral blood leukocytes were **incubated** together with Escherichia coli, Hanks balanced salt soln., and homologous serum; the addn. of I or superoxide dismutase inhibited cell death and lysis, whereas xanthosine-2H2O or choline chloride were ineffective. I (0.2 mg/mL) administered in the drinking water was used to treat coxsackie virus-induced myocarditis in mice. I also **reversed** the **toxic effects** of ionizing radiation (Co source) in mice and stimulated **lymphocyte** suppressor cell activity in mouse spleen cells. Na xanthosinate was used to treat adjuvant-induced arthritis in rats. I stimulated suppressor cell activity in expts. where Con-A exhibited a facilitator rather than suppressor-enhancing activity.

IT Immunomodulators
(xanthosine salts, polymorphic forms in relation to)

IT Inflammation inhibitors
(antiarthritics, xanthosine salts, polymorphic forms in relation to)

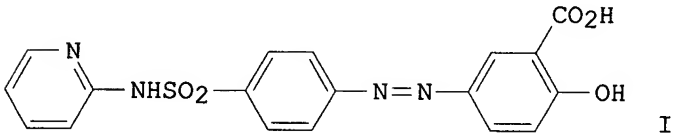
IT Radiation, biological effects
(ionizing, injury from, inhibition of, xanthosine salt polymorphs for)

IT 86018-10-2P 122431-04-3P 122431-05-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as immunomodulator, polymorphic forms in relation to)
IT 146-80-5DP, Xanthosine, salts
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as immunomodulators, polymorphic forms in relation to)

L20 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:95692 HCAPLUS
DOCUMENT NUMBER: 106:95692
TITLE: Biochemical basis for deoxyadenosine and 2-chlorodeoxyadenosine toxicity to resting human **lymphocytes**
AUTHOR(S): Seto, Shiro; Carrera, Carlos J.; Wasson, D. Bruce; Carson, Dennis A.
CORPORATE SOURCE: Dep. Basic Clin. Res., Scripps Clin. Res. Found., La Jolla, CA, USA
SOURCE: Advances in Experimental Medicine and Biology (1986), 195B(Purine Pyrimidine Metab. Man 5, Pt. B), 577-82
CODEN: AEMBAP; ISSN: 0065-2598
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Deoxyadenosine (I) [958-09-8] plus deoxycoformycin or 2-chlorodeoxyadenosine (II) [4291-63-8] alone induced DNA strand breaks in human resting peripheral blood **lymphocytes**. DNA strand breaks were apparent as early as 4 h after exposure to the deoxynucleosides; thereafter, the disintegration of DNA proceeded progressively. At 24 h of **incubation**, 10 .mu.M I plus 1 .mu.M deoxycoformycin or 10 .mu.M II produced DNA strand breakage (or alkali labile sites), almost equiv. to the amt. caused by 500 rads .gamma.-irradn. The DNA damage was followed by a marked fall in intracellular NAD [53-84-9] levels at 8 h and a drop in ATP [56-65-5] pools at 24 h. The depletion of these essential metabolites preceded cell death. Both I and II inhibited repair radiation-induced damage to DNA. Addn. of nicotinamide [98-92-0] to the culture medium increased the levels of NAD and partially protected the cells against the toxicity of I. The role of pyridine nucleotide metab. in the toxicity of I is discussed.
IT **Lymphocyte**
(chlorodeoxyadenosine and deoxyadenosine toxicity to human, NAD in)
IT 53-84-9, NAD 56-65-5, ATP, biological studies
RL: BIOL (Biological study)
(toxicity of chlorodeoxyadenosine and deoxyadenosine to human **lymphocytes** in relation to)
IT 98-92-0, Nicotinamide 110-86-1D, Pyridine, nucleotides
RL: BIOL (Biological study)
(**toxicity** of chlorodeoxyadenosine and deoxyadenosine to human **lymphocytes reversal** by, NAD in relation to)
IT 958-09-8, Deoxyadenosine 4291-63-8, 2-Chlorodeoxyadenosine
RL: PRP (Properties)

(toxicity of, to **lymphocytes** of humans, NAD in)

L20 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:515910 HCAPLUS
DOCUMENT NUMBER: 103:115910
TITLE: Sulfasalazine and derivatives, natural killer activity and ulcerative colitis
AUTHOR(S): Gibson, P. R.; Jewell, D. P.
CORPORATE SOURCE: Gastroenterol. Unit, Radcliffe Infirm., Oxford, UK
SOURCE: Clinical Science (1985), 69(2), 177-84
CODEN: CSCIAE; ISSN: 0143-5221
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The effects of sulfasalazine (I) [599-79-1], 5-aminosalicylic acid (5-ASA) [89-57-6], sulfapyridine [144-83-2], and azodisalicylic acid (ADS) [50984-80-0] in vitro on the natural killer (NK) activity of human peripheral blood mononuclear cells (MNC) were examd. and compared with those of the lipoxygenase [9029-60-1] inhibitor, nordihydroguaiaretic acid (NDGA) [500-38-9], and the cyclooxygenase [39391-18-9] inhibitor, indomethacin [53-86-1]. I, sulfapyridine and ADS inhibited NK activity with 50% inhibitory concns. (IC50) of 0.7, 2.5 and 4.0 mmol/L, resp.; the effect was rapidly **reversible**. In contrast, 5-ASA minimally inhibited NK activity at 50 mmol/L only. NDGA potently inhibited NK activity (IC50 27 .mu.mol/L) but this was only partly **reversible** in short-term **incubations**. Indomethacin had no effect at concns. less than those inhibiting cyclooxygenase activity (10-10 .mu.mol/L) but potently and **reversibly** inhibited NK activity at or above 25 .mu.mol/L. The inhibitory effects obsd. were unlikely to be due to direct **toxicity** of **effector** cells as 5-ASA, sulfapyridine and ADS had no effect on the viability of peripheral blood MNC, whereas NDGA and indomethacin lysed MNC only at maximal concns. tested. Though I produced MNC lysis at concns. .gtoreq. mmol/L, the rapid **reversibility** of the inhibition of NK activity at 1 mmol/L suggested that lysis of NK cells contributed little to the suppressive effect at this concn. The disparity of the therapeutic efficacy and effects on NK activity of I and its derivs. in vitro may suggest that NK activity is not a major pathogenic mechanism in ulcerative colitis. Any inhibitory effect on cellular immune function of indomethacin does not necessarily reflect an effect of cyclooxygenase inhibition.

IT Leukocyte
(mononuclear, natural killer activity of human, sulfasalazine and its derivs. effect on)

IT **Lymphocyte**

(natural killer, sulfasalazine and its derivs. effect on, of humans)
IT Intestine
(ulcerative colitis, pathogenesis of, natural killer activity of mononuclear cells and cyclooxygenase and lipoxygenase in relation to, of humans)
IT 39391-18-9
RL: BIOL (Biological study)
(inhibition of, by indomethacin, natural killer cell activity of mononuclear cells of humans response to)
IT 9029-60-1
RL: BIOL (Biological study)
(inhibition of, by nordihydroguaiaretic acid, natural killer cell activity of mononuclear cells of humans response to)
IT 53-86-1 89-57-6 144-83-2 500-38-9 599-79-1 599-79-1D, derivs. 50984-80-0
RL: BIOL (Biological study)
(natural killer cell activity of mononuclear cells of humans response to)

L20 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:421896 HCAPLUS
DOCUMENT NUMBER: 101:21896
TITLE: Increased adenosine deaminase (ADA) activity and a shift from ADA-dependent to ADA-independent phases during T-cell activation: a paradox
AUTHOR(S): Veit, Bruce C.; Fishman, Marvin; Look, Thomas
CORPORATE SOURCE: Div. Immunol., St. Jude Child. Res. Hosp., Memphis, TN, 38101, USA
SOURCE: JNCI, Journal of the National Cancer Institute (1984), 72(5), 1151-9
CODEN: JJIND8; ISSN: 0198-0157
DOCUMENT TYPE: Journal
LANGUAGE: English
AB During activation of WF rat splenic T-cells, a change occurs with respect to susceptibility to a toxic accumulation of adenosine or deoxyadenosine (dADO) in the presence of adenosine deaminase (ADA) blockade. Addn. of nucleoside 1 h after the initiation of a concanavalin A response in the presence of 2'-deoxycoformycin (DCF) markedly inhibited the response, whereas delay of addn. of the nucleoside for 24-48 h resulted in minimal or no inhibition. Inhibition was not simply the result of prolonged **incubation** of cells in the presence of nucleoside and was apparently not attributable to an effect on proliferating cells. Addn. of interleukin 2 (IL-2) to cultures contg. DCF and dADO did not **reverse** the inhibitory effect, which suggests that IL-2-producing T-cells also were not the target of nucleoside **toxicity**. A 2-fold increase in ADA activity that occurred during T-cell activation was nonessential for the survival of mitogen-activated T-cells in the presence of toxic concns. of dADO and did not account for an apparent increased resistance of these cells to nucleoside toxicity. These paradoxical observations prompted an anal. of ADA activity in various populations of activated T-cells enriched with cells in G0/G1, S, or G2+M cell-cycle phases, which indicated that increased ADA activity was not assocd. with a specific period during cell cycle traverse, but, rather, coincided with cell enlargement in prepn. for mitosis. In conclusion, either an early event in T-cell mitogenesis is highly

Ŕ, 30 h before spleen collection) of CD2F1 mice, in vitro **incubation** of spleen cells with I (25, 50, or 100 .mu.g/mL) reversed the irradn. induced decrease of cytotoxic T cell generation, the most active concn. being 25 .mu.g/mL. Cyclophosphamide (II) [50-18-0] (170 mg/kg) moderately, and (200 or 230 mg/kg) more markedly suppressed cytotoxic T cell generation by spleen of CD2F1 mice. I reversed this effect of II. The possible mechanisms of these effects are discussed.

IT Gamma ray, biological effects
(cytotoxic T cell formation by spleen suppression by, thymus hormones reversal of)

IT Spleen
(**lymphocyte** T cytotoxic cells formation by, cyclophosphamide and .gamma.-rays inhibition of, thymus hormones reversal of)

IT Immunosuppression
(thymus hormones reversal of)

IT **Lymphocyte**
(T-, cytotoxic, formation of, cyclophosphamide and .gamma.-rays inhibition of, thymus hormones reversal of)

IT Thymus hormones
RL: BIOL (Biological study)
(hypocalcemic, cytotoxic T cells formation abrogation by cyclophosphamide and .gamma.-rays reversal by)

IT 50-18-0
RL: BIOL (Biological study)
(cytotoxic T cell formation by spleen suppression by, thymus hormones reversal of)

L20 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1978:146915 HCAPLUS
DOCUMENT NUMBER: 88:146915
TITLE: Toxicity of organotin compounds. II. Comparative in vivo and in vitro studies with various organotin and organolead compounds in different animal species with special emphasis on **lymphocyte** cytotoxicity
AUTHOR(S): Seinen, Willem; Vos, Joseph G.; Van Spanje, Ine; Snoek, Margriet; Brands, Ruud; Hooykaas, Herbert
CORPORATE SOURCE: Fac. Vet. Sci., Univ. Utrecht, Utrecht, Neth.
SOURCE: Toxicology and Applied Pharmacology (1977), 42(1), 197-212
CODEN: TXAPA9; ISSN: 0041-008X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of organotin and organolead compds. were fed to male and female weanling rats for 2 wk at dietary levels of 0, 50, or 150 ppm, in order to evaluate their **toxic effects**, with special emphasis on the thymus and peripheral lymphoid organs. A dose-related redn. in the wt. of thymus, spleen, and popliteal lymph node, assocd. with **lymphocyte** depletion in the cortex of the thymus and the thymus-dependent areas in the peripheral lymphoid organs, was obsd. in animals fed di-n-octyltin dichloride (DOTC) [3542-36-7] and di-n-butyltin dichloride (DBTC) [683-18-1]. As shown previously, these effects were not related to stress. Similar, but less pronounced, lymphoid organ changes occurred in animals fed diets contg. diethyltin dichloride (DETC) [866-55-7] and di-n-propyltin dichloride [867-36-7]. In contrast,

other dialkyltin compds. (dimethyltin dichloride [753-73-1]; di-n-dodecyltin dibromide [65264-08-6]; and di-n-octadecyltin dibromide [65264-09-7]), as well as mono-n-octyltin trichloride (MOTC) [3091-25-6], tri-n-octyltin chloride [2587-76-0], and tetraoctyltin [3590-84-9] did not cause atrophy of lymphoid organs. Of the dialkyllead compds. tested, di-n-butyllead diacetate [2587-84-0] and di-n-hexyllead diacetate [18279-21-5], the latter caused distinct lymphoid atrophy, but only when assocd. with severe growth retardation. A similar structure-activity relation regarding thymus atrophy by dialkyltin compds. was obsd. after i.v. application. DOTC and DBTC were effective at a dose of 1 mg/kg. A dose-related decrease of thymus wt., cell count, and cell viability occurred in rats after a single i.v. injection of 0, 1, 2, 4, or 8 mg of DOTC/kg. The effect of DOTC was completely **reversible** . In contrast to rats, lymphoid atrophy did not occur in mice, guinea pigs, or Japanese quail fed DOTC or DBTC. In vitro **incubation** of thymocytes and bone marrow cells with DBTC and DOTC revealed the same selectivity regarding cell type and species origin of cells as was found in vivo. A dose-related decrease in the survival of rat thymocytes was obsd., whereas rat bone marrow cells were not affected by DBTC and DOTC at levels up to 50 .mu.g/mL. In contrast, the no. and viability of mouse and guinea pig thymocytes exposed to DBTC were the same as the controls. As the survival of human thymocytes was markedly decreased by DBTC, it possibly acts in the same manner in man and rat. In agreement with in vivo results, the survival of rat thymocytes was not significantly decreased by dimethyltin dichloride and diethyltin dichloride.

IT Toxicity
(of organolead and organotin compds., species in relation to)

IT **Lymphocyte**
(organolead and organotin compds. toxicity to)

IT Molecular structure-biological activity relationship
(lymphocytotoxic, of organolead and organotin compds.)

IT 683-18-1 753-73-1 866-55-7 867-36-7 2587-76-0 2587-84-0 3091-25-6 3542-36-7 3590-84-9 7439-92-1D, alkyl compds. 7440-31-5D, alkyl compds. 18279-21-5 65264-08-6 65264-09-7
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity of, species in relation to)

L20 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1976:133474 HCAPLUS
DOCUMENT NUMBER: 84:133474
TITLE: The influence of dissolved oxygen on the mitogen responses of mouse **lymphocytes**
AUTHOR(S): Kilburn, D. G.; Morley, M.; Yensen, J.
CORPORATE SOURCE: Dep. Microbiol., Univ. British Columbia, Vancouver, BC, Can.
SOURCE: Journal of Cellular Physiology (1976), 87(3), 307-11
CODEN: JCLLAX; ISSN: 0021-9541
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mouse spleen cells **incubated** at either 30 mm Hg dissolved O partial pressure (pO2) or 160 mm Hg did not differ significantly in their survival or in their proliferative response to the mitogens concanavalin A, phytohemagglutinin, or bacterial endotoxin in a

subsequent static culture. If the mitogen was added prior to exposing the cells to the controlled dissolved O environment, the incorporation of thymidine was always substantially lower in cells held at 160 mm Hg pO2. This **toxic effect** of O increased with the time of **incubation** and was not **reversed** by the inclusion of 2-mercaptoethanol in the medium. **Incubation** of cells with mitogen in the absence of O had no deleterious effect on the proliferative response. A comparison of DNA, RNA, and protein synthesis in concanavalin A-stimulated cells indicated that the predominant effect of O was on DNA synthesis.

IT Toxins
RL: BIOL (Biological study)
(bacterial, **lymphocyte** response to, oxygen effect on)

IT Deoxyribonucleic acids
Proteins
Ribonucleic acids
RL: FORM (Formation, nonpreparative)
(formation of, by mitogen-induced **lymphocytes**, oxygen effect on)

IT Mitogens
(**lymphocyte** response to, oxygen effect on)

IT Phytohemagglutinins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**lymphocyte** response to, oxygen effect on)

IT **Lymphocyte**
(mitogen induction of, oxygen effect on)

IT 7782-44-7, biological studies
RL: BIOL (Biological study)
(**lymphocyte** response to mitogens in relation to)

IT 11028-71-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**lymphocyte** response to, oxygen effect on)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, TOXCENTER, PHIC, PHIN, FSTA, CABA, AGRICOLA' ENTERED AT 11:50:49 ON 05 FEB 2003)

L1	9691	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	INCUBAT? AND LYMPHOCYTE
L8	103	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	L1 AND TOXIC?(5A)EFFECT?
L9	11	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	L8 AND (AMELIORAT? OR REVERS?)
L10	45	SEA	L9		
L15	3105	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	INCUBAT?(S)LYMPHOCYTE
L16	4232	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	TOXIC?(S)(AMELIORAT? OR REVERS?)
L17	1	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	L15 AND L16
L22	78	SEA	L17		
L23	107	S	L10 OR L22		
L24	41	DUP REM	L23 (66 DUPLICATES REMOVED)		

Searcher : Shears 308-4994

L24 ANSWER 1 OF 41 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-547698 [58] WPIDS
DOC. NO. NON-CPI: N2002-433605
DOC. NO. CPI: C2002-155299
TITLE: Novel isolated T-lymphocyte costimulatory polypeptide, such as CD28 related protein-1 or B7 related protein-1, useful for treating, preventing or ameliorating a T-cell mediated disorder in an animal.
DERWENT CLASS: B04 D16 P14 S03
INVENTOR(S): BLADT, A T; MAK, T W; SENALDI, G; SHAHINIAN, A; YOSHINAGA, S K
PATENT ASSIGNEE(S): (AMGE-N) AMGEN CANADA INC; (AMGE-N) AMGEN INC
COUNTRY COUNT: 99
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002044364	A2	20020606	(200258)*	EN	197
AU 2002017969	A	20020611	(200264)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002044364	A2	WO 2001-US44859	20011128
AU 2002017969	A	AU 2002-17969	20011128

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2002017969	A	Based on	WO 200244364

PRIORITY APPLN. INFO: US 2000-728420 20001128
AN 2002-547698 [58] WPIDS
AB WO 200244364 A UPAB: 20021031
NOVELTY - An isolated T-lymphocyte costimulatory polypeptide (I), such as CD28 related protein-1 (CRP1) or B7 related protein-1 (B7RP1), comprising a sequence (S1) of 200, 322, 288 or 302 amino acids fully defined in the specification, a mature form of S1, a fragment of S1, an ortholog of the above mentioned sequences, or an allelic variant or alternative slice variant of the above mentioned sequences, is new.

DETAILED DESCRIPTION - An isolated T-lymphocyte costimulatory polypeptide (I) comprises a sequence (S1) of 200, 322, 288 or 302 amino acids fully defined in the specification, a mature form of S1 comprising a mature amino terminus at residue 21 of the 200 amino acid sequence, at residue 47 of the 322 amino acid sequence, or at residues 19, 20, 21, 22, 24 or 28 of the 288 or 302 amino acid

sequence, a fragment of S1 comprising at least about 25, 50, 75, 100 or greater than 100 amino acid residues, an ortholog of the above mentioned sequences, or an allelic variant or alternative slice variant of the above mentioned sequences.

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid molecule comprising a sequence selected from a sequence (S2) of 600, 966, 864 or 1294 base pairs fully defined in the specification, a sequence encoding the polypeptide from residues 1-200 or 21-200 of the 200 amino acid sequence, a sequence encoding residues 1-322 or 47-322 of the 322 amino acid sequence, a sequence encoding residues 1-288, 19-288, 20-288, 21-288, 22-288, 24-288 or 28-288 of the 288 amino acid sequence, or a sequence encoding residues 19-302, 20-302, 21-302, 22-302, 24-302 or 28-302 of the 302 amino acid sequence, a sequence encoding a polypeptide that is at least about 70% identical to S1, a naturally occurring allelic variant, alternate splice variant or complement of the above mentioned sequences, a sequence encoding a polypeptide fragment of at least about 25, 50, 75, 100 or greater than 100 amino acids residues, a sequence comprising a fragment of at least about 10, 15, 20, 25, 50, 75, 100 or greater than 100 nucleotides, and a sequence which hybridizes under stringent to the above mentioned sequences;

(2) a host cell (III) comprising (II);

(3) production of (I);

(4) a polypeptide produced by the above mentioned method or encoded by (I);

(5) an antibody (IV) or its fragment that specifically binds to (I);

(6) a composition (V) comprising (I) and a pharmaceutically acceptable carrier, adjuvant, solubilizer, stabilizer or anti-oxidant;

(7) a polypeptide (VI) comprising a derivative of (I);

(8) a fusion polypeptide (VII) comprising (I) fused to a heterologous amino acid sequence;

(9) a transgenic non-human mammal (VIII) comprising (II);

(10) enhancing (M1) an immune response by administering B7RP1, or an agonist of CRP1 or B7RP1; and

(11) treating (M2) cancer or viral infection by administering B7RP1 or an agonist of CRP1, optionally in combination with B7.1 or B7.2.

ACTIVITY - Antiasthmatic; Antiallergic; Cytostatic; Virucide; Antirheumatic; Antiarthritic; Antipsoriatic; Neuroprotective; Antidiabetic; Dermatological; Immunosuppressive; Antiinflammatory; Antibacterial.

MECHANISM OF ACTION - Regulator of T-cell activation or proliferation in an animal; modulator of immune response; CRP1 or B7RP1 antagonist; inhibitor of IgE production (claimed); gene therapy. The in vitro inhibitory activity of isolated T-**lymphocyte** costimulatory polypeptide, such as B7 related protein-1 (B7RP1) fusion protein on ConA-stimulated T-**lymphocytes** was tested. Mouse splenocytes were prepared and enriched for T-**lymphocytes** by negative selection. 200000 splenocytes were used in T-cell proliferation assays in a 96-well round-bottom plate. Cells were **incubated** for 1 hour with media, CD28 related protein-1 (CRP-1)Fc, B7RP1-Fc, or B7.2-Fc, fusion proteins. Media (no adds), or Con A at various concentrations were added. The cells were then **incubated**. After 42 hour, cells were pulsed with 3H-thymidine for 6 hours, harvested and

incorporated radioactivity was determined. The Fc fusion proteins did not demonstrate significant T-cell stimulatory or inhibitory activity by themselves, however, in the presence of 1 micro g/ml and 3 micro g/ml Con A, both the B7RP1-Fc and the known B7.2-Fc fusion proteins showed significant inhibitory activity. At high concentration (10 micro g/ml), Con A stimulation resulted in cell death. Addition of either B7RP1-Fc or B7.2-Fc, significantly protected the cells from the detrimental effects of high concentrations of Con A. In both inhibitor and protective functions, the effect by B7RP1-Fc protein was greater than B7.2-Fc protein on the Con A stimulated cells. These data indicated that the B7RP1 protein functioned to regulate T-cell proliferation.

USE - (I) is useful for treating, preventing or **ameliorating** a T-cell mediated disorder in an animal. (I) is useful for diagnosing a T-cell mediated disorder or a susceptibility to a T-cell mediated disorder in an animal, by determining the presence or amount of expression of (I), and diagnosing a T-cell mediated disorder or a susceptibility to a T-cell mediated disorder based on the presence or amount of expression of (I). (I) is useful for identifying a test molecule which binds to (I) by contacting (I) with a test molecule, and determining the extent of binding of (I) to the test molecule. The method further comprises determining the activity of (I) when bound to the compound. (II) is useful for regulating T-cell activation or proliferation in an animal. (IV) is useful for suppressing an immune response in an animal, for decreasing IgE production in an animal or for treating an IgE-mediated disorder such as asthma or allergic disorder. (IV) is an antagonist of CRP1 or B7RP1, where (IV) binds B7RP1 or CRP1 and partially or completely inhibits IgE production. The method further comprises administering IgE antagonist such as an anti-IgE antibody. M1 is useful for enhancing an immune response. M2 is useful for treating cancer or viral infection (all claimed). (I) is useful for preparing (IV), and in the treatment of immune disease, graft survival, immune activation, T-cell dependent B-cell mediated disease and cancer gene immune therapy. (II) is useful as hybridization probes in diagnostic assays, and in gene therapy. (IV) is useful for treating autoimmune disorders (such as rheumatoid arthritis, psoriasis, multiple sclerosis, diabetes and systemic lupus erythematosus), **toxic** shock syndrome, bone marrow and organ transplantation, inflammatory bowel disease, allosensitization due to blood transfusions, and the treatment of graft vs. host disease, and for regulating the interaction of B7RP1 or CRP1.

Dwg.0/23

L24 ANSWER 2 OF 41	TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER:	2002:69008 TOXCENTER
COPYRIGHT:	Copyright 2003 ACS
TITLE:	Brief triphenyltin exposure causes irreversible inhibition of the cytotoxic function of human natural killer cells
AUTHOR(S):	Wilson, Sharnise; Loganathan, Bommanna G.; Whalen, Margaret M.
CORPORATE SOURCE:	Department of Chemistry, Tennessee State University, Nashville, TN, 37209, USA.
SOURCE:	Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002, (2002) pp. ENVR-166.

CODEN: 69CKQP.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Conference
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2002:188851
LANGUAGE: English
ENTRY DATE: Entered STN: 20020319
Last Updated on STN: 20020319

AB Phenyltin (PT) contamination has been reported in water, sediment, and fish. Triphenyltin (TPT) has been implicated in a wide spectrum of **toxic effects** in exposed animals, including increased tumor formation. Human exposure to TPT might come from occupational exposure as well as consumption of contaminated food. Natural Killer cells are a primary immune defense against tumor and virally infected cells. Previously, we reported that exposure to TPT significantly inhibited the tumor killing capacity of human NK cells. In this study we examine whether the inhibition of NK-cell cytotoxicity induced by a 1 h exposure to TPT is **reversible**, when the cells are allowed to recover in TPT-free media for up to 6 days. The results revealed that exposure to 750 nM TPT for 1h caused a 57% decrease in NK-cytotoxic function. However, if the cells were allowed to **incubate** in TBT-free media for 24 h there was an 84% inhibition of NK cytotoxicity. There was no significant recovery of NK-cytotoxic function when the **lymphocytes** were allowed to **incubate** in TPT-free media for up to 6 days. The results indicated that short-term exposure to TPT caused persistent neg. effects on NK-cell ability to kill cancer cells.

L24 ANSWER 3 OF 41 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001161472 MEDLINE
DOCUMENT NUMBER: 21159349 PubMed ID: 11259095
TITLE: Decrease of breast cancer cell invasiveness by sodium phenylacetate (NaPa) is associated with an increased expression of adhesive molecules.
AUTHOR: Vasse M; Thibout D; Paysant J; Legrand E; Soria C; Crepin M
CORPORATE SOURCE: Laboratoire DIFEMA, Groupe de Recherche MERCI, Faculte de Medecine et Pharmacie de Rouen, 22 Bd Gambetta, 76183 Rouen Cedex, France.
SOURCE: BRITISH JOURNAL OF CANCER, (2001 Mar 23) 84 (6) 802-7.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: Scotland: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503

AB Sodium phenylacetate (NaPa), a non-**toxic** phenylalanine metabolite, has been shown to induce in vivo and in vitro cytostatic and antiproliferative effects on various cell types. In this work, we analysed the effect of NaPa on the invasiveness of breast cancer cell (MDA-MB-231, MCF-7 and MCF-7 ras). Using the highly invasive breast cancer cell line MDA-MB-231, we demonstrated that an 18-hour **incubation** with NaPa strongly inhibits the cell invasiveness

through Matrigel (86% inhibition at 20 mM of NaPa). As cell invasiveness is greatly influenced by the expression of urokinase (u-PA) and its cell surface receptor (u-PAR) as well as the secretion of matrix metalloproteinases (MMP), we tested the effect of NaPa on these parameters. An 18-hour **incubation** with NaPa did not modify u-PA expression, either on MDA-MB-231 or on MCF-7 and MCF-7 ras cell lines, and induced a small u-PA decrease after 3 days of treatment of MDA-MB-321 with NaPa. In contrast, an 18 h **incubation** of MDA-MB-231 increased the expression of u-PAR and the secretion of MMP-9. As u-PAR is a ligand for vitronectin, a composant of the extracellular matrix, these data could explain the increased adhesion of MDA-MB-231 to vitronectin, while cell adhesivity of MCF-7 and MCF-7 ras was unmodified by NaPa treatment. NaPa induced also an increased expression of both **Lymphocyte** Function-Associated-1 (LFA-1) and Intercellular Adhesion Molecule-1 (ICAM-1), which was obvious from 18 hour **incubation** with NaPa for the MDA-MB-231 cells, but was delayed (3 days) for MCF-7 and MCF-7 ras. Only neutralizing antibodies against LFA-1 **reversed** the decreased invasiveness of NaPa-treated cells. Therefore we can conclude that the strong inhibition of MDA-MB-231 invasiveness is not due to a decrease in proteases involved in cell migration (u-PA and MMP) but could be related both to the modification of cell structure and an increased expression of adhesion molecules such as u-PAR and LFA-1.

L24 ANSWER 4 OF 41 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001440273 MEDLINE
DOCUMENT NUMBER: 21378829 PubMed ID: 11485386
TITLE: Mercuric chloride enhances immunoglobulin E-dependent mediator release from human basophils.
AUTHOR: Strenzke N; Grabbe J; Plath K E; Rohwer J; Wolff H H; Gibbs B F
CORPORATE SOURCE: Department of Dermatology, Medical University of Lubeck, Lubeck, Germany.
SOURCE: TOXICOLOGY AND APPLIED PHARMACOLOGY, (2001 Aug 1) 174 (3) 257-63.
Journal code: 0416575. ISSN: 0041-008X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010903
Last Updated on STN: 20010903
Entered Medline: 20010830

AB Mercuric chloride (HgCl2) is an industrial agent known to cause autoimmune disorders and induce IgE synthesis, which plays a crucial role in the manifestation of allergic diseases. In rodents, the immunomodulatory effects of HgCl2 have been shown to involve the enhancement of mast cell-derived IL-4 secretion, which facilitates both Th2-**lymphocyte** development and IgE production. In humans, rapid allergen-dependent release of IL-4 and the related cytokine IL-13 from histamine-containing cells occurs primarily in basophils, along with other proinflammatory mediators such as histamine and LTC4. In this study, we therefore investigated the effects of HgCl2 on the release of the above basophil mediators, either due to the compound alone or in conjunction with

IgE-dependent stimulation. HgCl2 (10(-9) to 10(-6) M) did not induce mediator secretion alone but significantly enhanced the release of histamine, LTC4, IL-4, and IL-13 caused by anti-IgE. Higher concentrations of HgCl2 (10(-5) to 10(-3) M) strikingly reduced cell viability; however, **toxicity** varied depending on cell density and **incubation** time. Removal of HgCl2 following a short **incubation** with basophils did not **reverse** the potentiating effects on basophil mediator secretion to anti-IgE and the concentration of free mercury in the supernatants significantly diminished by up to 20% after **incubation** with the cells, indicating irreversible Hg binding to cells. By upregulating IgE-dependent human basophil mediator release, our results clearly indicate that HgCl2 potentially exacerbates allergic disorders and promotes a Th2-cytokine profile.

L24 ANSWER 5 OF 41 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-601967 [57] WPIDS
DOC. NO. CPI: C2000-180133
TITLE: New mercaptosalicylhydrazides useful for preventing and treating HIV infection in mammals, by inhibiting human immunodeficiency virus type-I integrase.
DERWENT CLASS: B04 B05 C02 C03 D16
INVENTOR(S): BURKE, T; LIN, Z; NEAMATI, N; POMMIER, Y
PATENT ASSIGNEE(S): (USSH) US DEPT HEALTH & HUMAN SERVICES
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000053577	A1	20000914	(200057)*	EN	54

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000038754 A 20000928 (200067)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000053577	A1	WO 2000-US6361	20000310
AU 2000038754	A	AU 2000-38754	20000310

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000038754	A	Based on	WO 200053577

PRIORITY APPLN. INFO: US 1999-124302P 19990312
AN 2000-601967 [57] WPIDS
AB WO 200053577 A UPAB: 20001109
NOVELTY - Mercaptosalicylhydrazides (I) are new.
DETAILED DESCRIPTION - Mercaptosalicylhydrazides (I) and their

salts are new.

A = 2 mercapto substituted aromatic or aromatic heterocyclic ring system;

Y' = (un)substituted lower alkyl.

INDEPENDENT CLAIMS are also included for:

(1) a pharmaceutical composition comprising (I);

(2) the preparation of a medicament comprising (I);

(3) a pharmaceutical composition comprising (I) and an AIDS antiviral agent, an anti-infective agent and/or an immuno modulator;

(4) the preparation of bisthiosalicylhydrazide (BTSH) of (I); and

(5) a method for screening an anti-HIV integrase drug comprising assaying HIV integrase inhibition and utilizing the assay to screen for drugs inhibiting HIV integrase activity in the presence of Mg2+.

ACTIVITY - Anti-HIV. (I) was tested for anti-HIV activity. Mercaptosalicylhydrazides were dissolved in dimethyl sulfoxide and diluted 1:100 in cell culture medium. Exponentially growing T4 **lymphocytes** (CEM cell line) were added at 5000 cells per well. Frozen virus stock solutions were thawed immediately before use, suspended in complete medium to yield the desire multiplicity of infection and added to microtiter wells, resulting in a 1:200 final dilution of the compound. Uninfected cells with the compound served as a toxicity control, and infected and uninfected cells without the compound served as basic controls. Cultures were **incubated** at 37 deg. C in a 5% CO2 atmosphere for 6 days. The tetrazolium salt, XTT was added to all wells and cultures were **incubated** to allow formazan color development by viable cells. Individual wells were analyzed spectrophotometrically to quantitate formazan production, and in addition were viewed microscopically for detection of viable cells and confirmation of protective activity. N,N'-bis(2-mercaptobenzoyl)-2,2'-dithiosalicylhydrazide, N,N'-bis(2,2'-dithiosalicyl)hydrazide and N,N'-bis(2,2'-dithiosalicyl)hydrazide protected HIV-1 infected cells with 50 % inhibitory concentration (IC50) values ranging from 14-34 micro M and 50 % effective concentration (EC50) values ranging from 4-18 micro M. N,N'-bis-salicylhydrazide was cytotoxic and exhibited an IC50 value of 0.1 micro M without showing protection of the HIV-1 infected cells. There was a 300-fold reduction in cytotoxicity of mercaptosalicylhydrazides relative to 1.

MECHANISM OF ACTION - HIV type-1 integrase inhibitor (claimed).

USE - (I) or (I) in combination with other compounds such as AIDS antiviral agent, anti-infective agent or an immunomodulator is useful for preventing and treating HIV infection in mammals (claimed).

ADVANTAGE - Unlike other known salicylhydrazides, (I) is 300 fold less **toxic** and exhibits enhanced viral activity. (I) has no detectable effect on other retroviral targets, including **reverse** transcriptase, protease, and virus attachment and exhibit no detectable activity against human topoisomerase I at concentrations that effectively inhibited integrase. Unlike prior integrase inhibitor, (I) is active in the presence of both Mn2+ and Mg2+.

Dwg.0/8

L24 ANSWER 6 OF 41 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000099817 MEDLINE
DOCUMENT NUMBER: 20099817 PubMed ID: 10634000

TITLE: Depressed cytolytic activity of peripheral blood mononuclear cells in unusually high paclitaxel concentrations: reversal by IL-2 and IL-12.
AUTHOR: Chen Y M; Yang W K; Ting C C; Yang D M; Whang-Peng J; Perng R P
CORPORATE SOURCE: Department of Chest Department, Taipei Veterans General Hospital, Taiwan, ROC.
SOURCE: CHUNG-HUA I HSUEH TSA CHIH [CHINESE MEDICAL JOURNAL], (1999 Dec) 62 (12) 867-74.
Journal code: 0005327. ISSN: 0578-1337.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000128

AB BACKGROUND: Human **lymphocyte** function was inhibited by high concentrations of paclitaxel and the effect was **reversed** by interleukin (IL)-2. However, there was no parallel study determining the relationship between paclitaxel concentrations in the **lymphocyte** cultures and pharmacokinetic analysis in human patients, nor was there any study on the **reversal** by cytokines, other than IL-2, of the paclitaxel-induced suppression of **lymphocyte** cytotoxicity. METHODS: We tested the effect of different doses of paclitaxel with various **incubation** times on the cytolytic activity of peripheral blood mononuclear cells (PBMNCs) against K-562 target cells. RESULTS: Our results showed that using a schedule similar to that for treating patients with tolerable doses of paclitaxel, no inhibition of cytolytic activity of PBMNCs was seen. When the paclitaxel concentration was increased 10-fold, the cytolytic activity of PBMNCs was significantly reduced. This suppression was **reversed** by the simultaneous addition of a low dose (10 U/ml) of IL-2 or IL-12. Addition of granulocyte macrophage-colony stimulating factor (10 U/ml) did not affect the cytolytic activity of PBMNCs, whereas addition of IL-4 reduced it. Time kinetic studies revealed that, with the addition of IL-2 or IL-12, most of the mononuclear cellular cytolytic activity recovered within 48 to 72 hours. CONCLUSIONS: These findings suggested that, to reduce the **toxicity** on mononuclear cellular function when high-dose paclitaxel treatment is elected in clinical practice, paclitaxel should be infused over a longer duration of time, or the treatment should be combined with the administration of a low dose of IL-2 or IL-12.

L24 ANSWER 7 OF 41 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000142641 MEDLINE
DOCUMENT NUMBER: 20142641 PubMed ID: 10678151
TITLE: Suppressive effect of kanglemycin C on T- and B-lymphocyte activation.
AUTHOR: Li J M; Lin Z B
CORPORATE SOURCE: Department of Pharmacology, Beijing Medical University, China.
SOURCE: CHUNG-KUO YAO LI HSUEH PAO [ACTA PHARMACOLOGICA SINICA], (1999 Jun) 20 (6) 546-50.
Journal code: 8100330. ISSN: 0253-9756.

PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000512
Last Updated on STN: 20000512
Entered Medline: 20000501

AB AIM: To elucidate the suppressive effect of kanglemycin C (Kan) on **lymphocyte** proliferation and T-**lymphocyte** subsets. METHODS: Splenocyte proliferation was quantified with [3H]thymidine ([3H]TdR) pulsing method or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetery. L3T4+ and Lyt2+ T-cell subsets were measured with fluorescence-activated cell sorter (FACS). Splenocyte viability was assessed with trypan blue exclusion. RESULTS: Like ciclosporin (Cic), Kan 8, 40, 80, and 400 nmol.L-1 inhibited the proliferation of 20%-80% **incubated** mouse splenocytes stimulated by concanavalin A (Con A) 5 mg.L-1, phytohemagglutinin (PHA) 5 mg.L-1, tetradecanoylphorbol acetate (TPA) 10 micrograms.L-1 + ionomycin (IM) 0.5 mg.L-1, and alloantigen (mixed **lymphocyte** reaction). Kan had no **toxicity** to the splenocytes at the treated doses. Suppression by Kan was declined with addition time of Kan after culture onset. Furthermore, the suppressive effect of Kan on splenocyte proliferation stimulated by lipopolysaccharides (LPS) 10 mg.L-1 was similar to that on splenocyte proliferation mediated by Con A. Unlike Cic, Kan **reversed** the ratio of L3T4+/Lyt2+ T-cell subsets. CONCLUSION: Kan had a suppressive action on proliferation of T- and B-**lymphocytes** and had a selective effect on helper-inducer T-**lymphocyte** (Th) subset from Cic. Suppression by Kan was time-dependent and not associated with **toxicity** of Kan.

L24 ANSWER 8 OF 41 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998094618 EMBASE
TITLE: In vitro immunosuppressive activity, isolation from pig liver microsomes and identification by electrospray ms-ms of a new FK-506 C19-c20 epoxide metabolite.
AUTHOR: Lhoest G.; Dieden R.; Verbeeck R.K.; Maton N.; Ingendoh A.; Latinne D.
CORPORATE SOURCE: G. Lhoest, Dept. of Pharmaceutical Sciences, 7246, Av. E. Mounier, B-1200 Brussels, Belgium
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1998) 284/3 (1074-1081).
Refs: 23
ISSN: 0022-3565 CODEN: JPETAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In order to mediate their effects, cyclosporin A and FK-506 must each bind with high affinity to a cytosolic target protein that belongs to the immunophilin group. FK-506 forms complexes with the FK-506 binding protein FKBP, mainly FKBP-12, and these complexes possess immunosuppressive activity through their ability to interact

with another target, the abundant serine threonine phosphatase calcineurin. Evaluating the immunosuppressive activities of the FK-506 metabolites by comparing them with known immunosuppressive agents via mixed **lymphocyte** reaction is of clinical importance because some metabolites may retain the pharmacological activity of the parent drug or exhibit cytotoxic effects. FK-506 is metabolized by the cytochrome P-450-dependent mixed-function oxygenase system in different animal species, and we are reporting the isolation from pig liver microsomes, and the identification by electrospray ms-ms, of the FK-506 C19-C20 epoxide metabolite. We found that this new metabolite exhibits reduced in vitro immunosuppressive activity compared with FK-506 and has approximately the same immunosuppressive potency as other known immunosuppressive drugs, such as cyclosporin A and IMM-125, a hydroxyethyl derivative of D-serine cyclosporin A. We were able to demonstrate that after **incubation** of the FK- 506 metabolite in human mixed **lymphocyte** reaction cultures for 6 days, the compound was stable under the conditions used for call culture as evidenced by electrospray-ms data. A weak direct cytotoxic effect (<30% cell death) was observed only at the highest concentrations (2500 and 5000 ng/ml), which shows that the mixed **lymphocyte** reaction inhibition cannot be due to a **toxic effect.**

L24 ANSWER 9 OF 41 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97291260 MEDLINE
DOCUMENT NUMBER: 97291260 PubMed ID: 9145874
TITLE: 1592U89, a novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity.
AUTHOR: Daluge S M; Good S S; Faletto M B; Miller W H; St Clair M H; Boone L R; Tisdale M; Parry N R; Reardon J E; Dornsife R E; Averett D R; Krenitsky T A
CORPORATE SOURCE: Glaxo Wellcome Inc., Research Triangle Park, North Carolina 27709, USA.. susan_daluge@glaxo.com
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1997 May) 41 (5) 1082-93.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970902
Last Updated on STN: 19970902
Entered Medline: 19970821

AB 1592U89, (-)-(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclo pentene-1-methanol, is a carbocyclic nucleoside with a unique biological profile giving potent, selective anti-human immunodeficiency virus (HIV) activity. 1592U89 was selected after evaluation of a wide variety of analogs containing a cyclopentene substitution for the 2'-deoxyriboside of natural deoxynucleosides, optimizing in vitro anti-HIV potency, oral bioavailability, and central nervous system (CNS) penetration. 1592U89 was equivalent in potency to 3'-azido-3'-deoxythymidine (AZT) in human peripheral blood **lymphocyte** (PBL) cultures against clinical isolates of HIV type 1 (HIV-1) from antiretroviral drug-naive patients (average 50% inhibitory concentration [IC50], 0.26 microM for

1592U89 and 0.23 microM for AZT). 1592U89 showed minimal cross-resistance (approximately twofold) with AZT and other approved HIV **reverse** transcriptase (RT) inhibitors. 1592U89 was synergistic in combination with AZT, the nonnucleoside RT inhibitor nevirapine, and the protease inhibitor 141W94 in MT4 cells against HIV-1 (IIIB). 1592U89 was anabolized intracellularly to its 5'-monophosphate in CD4+ CEM cells and in PBLs, but the di- and triphosphates of 1592U89 were not detected. The only triphosphate found in cells **incubated** with 1592U89 was that of the guanine analog (-)-carbovir (CBV). However, the in vivo pharmacokinetic, distribution, and **toxicological** profiles of 1592U89 were distinct from and improved over those of CBV, probably because CBV itself was not appreciably formed from 1592U89 in cells or animals (<2%). The 5'-triphosphate of CBV was a potent, selective inhibitor of HIV-1 RT, with Ki values for DNA polymerases (alpha, beta, gamma, and epsilon which were 90-, 2,900-, 1,200-, and 1,900-fold greater, respectively, than for RT (Ki, 21 nM). 1592U89 was relatively nontoxic to human bone marrow progenitors erythroid burst-forming unit and granulocyte-macrophage CFU (IC50s, 110 microM) and human leukemic and liver tumor cell lines. 1592U89 had excellent oral bioavailability (105% in the rat) and penetrated the CNS (rat brain and monkey cerebrospinal fluid) as well as AZT. Having demonstrated an excellent preclinical profile, 1592U89 has progressed to clinical evaluation in HIV-infected patients.

L24 ANSWER 10 OF 41 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97114029 MEDLINE
DOCUMENT NUMBER: 97114029 PubMed ID: 8955849
TITLE: Inhibition of HIV replication by immunoliposomal antisense oligonucleotide.
AUTHOR: Selvam M P; Buck S M; Blay R A; Mayner R E; Mied P A; Epstein J S
CORPORATE SOURCE: Center for Biologics, Evaluation and Research, US Food and Drug Administration, Rockville, MD 20852, USA.. Selvam@al.cher.fda.gov
SOURCE: ANTIVIRAL RESEARCH, (1996 Dec) 33 (1) 11-20. Journal code: 8109699. ISSN: 0166-3542.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19970414
Entered Medline: 19970328

AB The sequence-specific suppression of HIV-1 replication using CD4 monoclonal-antibody-targeted liposomes, containing Rev antisense phosphorothioate oligonucleotides is described. Liposomes were prepared by encapsulating the 20-mer antisense DNA sequence of the rev HIV-1 regulatory gene, in the form of a phosphorothioate oligonucleotide. Specific targeting was accomplished by conjugating anti-CD4 mouse monoclonal antibody to the surface of the liposomes. HIV-1-infected H9 cells as well as peripheral blood T-**lymphocytes** were **incubated** with the immunoliposomes of antisense found to have potential antiviral effect. HIV-1 replication was reduced by 85% in antisense immunoliposome-treated H9 cells and peripheral blood **lymphocytes**, whereas the inhibition of HIV-1 replication was

not observed using either empty immunoliposomes or immunoliposomes containing scrambled Rev phosphorothioate oligonucleotide sequences. The antiviral activity of both the free and the encapsulated oligonucleotides were assessed by p24, **reverse** transcriptase (RT) assays and polymerase chain reaction (PCR) analysis. Liposome preparations demonstrated minimal **toxicity** in H9 as well as in peripheral blood **lymphocyte** cell culture experiments. These in vitro culture results demonstrate the potential efficacy of immunoliposomes to inhibit HIV replication.

L24 ANSWER 11 OF 41 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 96:57886 SCISEARCH
THE GENUINE ARTICLE: TN432
TITLE: VLA-6 (CDW49F) IS AN IMPORTANT ADHESION MOLECULE IN NK CELL-MEDIATED CYTOTOXICITY FOLLOWING AUTOLOGOUS OR ALLOGENEIC BONE-MARROW TRANSPLANTATION
AUTHOR: LOWDELL M W (Reprint); SHAMIM F; HAMON M; MACDONALD I D; PRENTICE H G
CORPORATE SOURCE: ROYAL FREE HOSP, SCH MED, DEPT HAEMATOL, BMT UNIT, LONDON NW3 1YD, ENGLAND (Reprint); DERRIFORD HOSP, DEPT HAEMATOL, PLYMOUTH, DEVON, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: EXPERIMENTAL HEMATOLOGY, (DEC 1995) Vol. 23, No. 14, pp. 1530-1534.
ISSN: 0301-472X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 14

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Graft-vs.-leukemia (GVL) is postulated to be the principal mechanism responsible for continued remission after allogeneic bone marrow transplantation (BMT). The specific cytotoxic effecters mediating this effect are as yet undefined, but the major histocompatibility complex (MHC)-nonrestricted lysis of tumor cell lines by natural killer (NK) and lymphokine-activated killer (LAK) cells from recipients of allogeneic BMTs has been proposed as an in vitro correlate of GVL.

In vitro culture or treatment in vivo with interleukin-2 (IL-2) is associated with enhanced NK cytotoxicity and lysis of NK-resistant targets (LAK cytotoxicity). NK, LAK, and cytotoxic T **lymphocytes** (CTL) have cytotoxic properties against autologous and allogeneic leukemic targets. These immune effector cells require receptor-ligand interaction for target recognition and adhesion via specific molecules such as integrins, a group of heterodimeric transmembrane glycoproteins. The integrins include the very late activation (VLA) subfamily, which all share the same beta(1) subunit but have distinct chains. VLA-6 (CDw49f) has been identified on NK cells and binds to laminin, a basement membrane protein found on malignant tumor cells but not normal cells. Monoclonal antibodies (mAbs) to laminin have been found to inhibit in vitro cytotoxicity of the tumor cell line K562, suggesting an important role for VLA-6 in this interaction. The specific aim of this study was to investigate the role of VLA-6 in the interactions of the tumor cell lines K562 and Daudi with peripheral blood **lymphocytes** (PBL) acting as **effecters** in cell-mediated cyto; **toxicity** from normal volunteers,

patients recovering from chemotherapy, and patients recovering from autologous or allogeneic BMT.

In over 96% of assays, **incubation** of effector cells with anti-CDw49f mAbs led to detectable inhibition of NK and LAK cell-mediated cytotoxicity. More notably, the degree of anti-VLA6-induced suppression of LAK activity was significantly greater in the normal donors than in any of the patient groups, despite a significantly lower incidence of expression of VLA-6 on NK cells from controls than from patients. This implies a reduced role for this adhesion molecule in LAK activity following some form of in vivo stimulation. This hypothesis is supported by the observation that addition of exogenous IL-2 to the cultures **ameliorated** the effect of VLA-S blockade, although the incidence and level of VLA-6 expression was unchanged by IL-2. In contrast, VLA-6 blocking led to a greater reduction in NK activity of BMT recipients than of normal donors, demonstrating that the VLA-6 adhesion pathway is important in this group of patients. These results indicate that the VLA-6-laminin interaction is important in normal NK-target interaction but may play a less significant role in the innate cytotoxic response post-BMT, perhaps reflecting subtle differences in the subsets of NK cells present in BMT recipients compared with normal donors.

L24 ANSWER 12 OF 41 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:623743 TOXCENTER
DOCUMENT NUMBER: RISKLINE-1996090002
TITLE: Butoxyethanol criteria document. Including a supplement for 2-Butoxyethyl acetate
AUTHOR(S): ECETOC working group
SOURCE: ECETOC Special report, (1994) 7 71 p.
FILE SEGMENT: RISKLINE
LANGUAGE: English
ENTRY DATE: Entered STN: 20021200
Last Updated on STN: 20021200

AB Because of the uncertainties of extrapolating from animals to man, adequate human data should take precedence over animal data for developing human exposure standards. There is a considerable data base of human acute studies with 2-butoxyethanol. Human Inhalation Exposure Studies with 2-Butoxyethanol. Haemolysis appears to be the primary, most sensitive indicator of 2-butoxyethanol toxicity in animals. This is an acute effect, often **reversing** with continued low exposure. Although no subchronic exposure studies have been performed in man, there are human acute exposure studies which were considered in this assessment. There was no reported evidence of haemolysis, osmotic fragility (a precursor to haemolysis), or other systemic **toxic effects** when male and female human volunteers were exposed to either 1 00 or 195 ppm of 2-butoxyethanol for 8 h (Carpenter et al, 1956). It is relevant that haemoglobinuria was reported in rats exposed under the same conditions. The volunteers complained of discomfort from irritancy to the nose and eyes at both concentrations, and some individuals reported nausea and headache. No irritancy, evidence of haemolysis (haemoglobinuria) nor other adverse health effects were reported in male volunteers, while exercising tightly and exposed to 20 ppm 2-butoxyethanol for 2 h (Johanson et al, 1986a). No irritation, haemolysis or other systemic effects were reported in male volunteers exposed to 50 ppm 2-butoxyethanol vapour for 2 h (Johanson and Boman, 1991). The study compared uptake following

concurrent inhalation and dermal (whole body) exposure. Each exposure period lasted for 2 h, and was separated by a one hour rest. The results demonstrate that adverse effects are unlikely in human beings, even under exaggerated physical conditions. Thus, human experience indicates that acute exposures to concentrations of 20 - 50 ppm are not overtly irritating. Concentrations of 100 ppm and above are clearly irritating and cause subjective toxic symptoms. Because of the relatively short half-life of 2-butoxyacetic acid in man, systemic retention from one workday to the next is considered unlikely. Determination of an animal NOEL. There are several studies in animals that have used inhalation, the route of concern for setting an indicative exposure value. It should be noted that all of these experiments involved whole body exposure to 2-butoxyethanol vapour. It therefore follows that the no effect levels so obtained reflect concurrent dermal and inhalation exposure to 2-butoxyethanol. A no effect level of 25 ppm (Dodd et al, 1983) reported when rats were exposed for 90 d, 6 h/d by inhalation, appears to be the most reliable. The LOEL was 77 ppm, and the effects reported at this concentration were indicative of intravascular haemolysis (decreased RBC counts and blood Hb). At higher concentrations (up to 245 ppm in a 9 day study) the reported effects included haemoglobinuria, increased reticulocyte and **lymphocyte** counts, decreased bw gain and increased liver weight. A 14 day recovery period showed substantial **reversal** of the blood parameters. In contrast, subchronic studies with species relatively insensitive to haemolysis have reported no effect levels (other than for respiratory irritation) as high as 107 ppm (Carpenter et al, 1956) and 125 ppm (Tyler, 1984) for guinea pig, and 100 ppm for dogs (Carpenter et al, 1956). No longer-term inhalation studies are currently available for 2-butoxyethanol. However, red cell haemolysis in susceptible species such as rats and mice is a transient phenomenon seen only on the first few days of exposure, not thereafter (Dodd et al, 1983; Grant et al, 1985; Tyl et al, 1984). This reflects repopulation of the blood with erythrocytes resistant to 2-butoxyacetic acid-induced haemolysis. Thus, it is considered unlikely that a lower NOEL for haemolysis would be obtained following long term exposure of rodents or other, non-sensitive species. Relevance of Haemolysis to Humans. Rats and mice are much more susceptible to 2-butoxyethanol-induced intravascular haemolysis than man. Humans beings exposed to concentrations as high as 200 ppm were not reported to exhibit haemoglobinuria, the initial most sensitive indicator of intravascular haemolysis (Carpenter et al, 1956). However, two human beings intentionally ingesting formulated product containing 2- butoxyethanol did exhibit haemoglobinuria and decreased RBC counts, as well as metabolic acidosis and coma (Rambourg-Schepens et al, 1988; Gijsenbergh et al, 1989). These results indicate that at sufficiently high oral doses, haemolysis can occur in man. Dose-response Relationship. The haemolytic effect of 2-butoxyethanol is mediated in vivo by its acid metabolise 2-butoxyacetic acid which causes swelling (a prehaemolytic effect) when rat RBC are **incubated** with 0.2 mM 2- butoxyacetic acid, and extensive haemolysis at 2 mM (Udden and Patton, 1994). Human RBCS, in comparison, are more resistant to these effects. Udden (1994) examined blood from several populations with a possible hypersusceptibility to 2-butoxyethanol-induced haemolysis. The blood samples came from elderly people, and sickle cell and hereditary spherocytosis patients. None exhibited haemolysis or

prehaemoiytic changes under conditions (2 mM 2-butoxyacetic acid) which readily haemolysed rat RBCS. There was increased cell volume with slight haemolysis in some individuals only at 8 mM 2-butoxyacetic acid (Ghanayem, 1989a). Thus, in vitro studies indicate that human red cells are at least 10 times, and may be up to 40 times less sensitive to 2- butoxyacetic acid-induced haemolysis than rat RBCS. Also, there appear to be no identified hypersusceptible populations of humans to 2-butoxyethanol-induced haemolysis. Assessing a safe human dose. Assessing a safe human dose involves taking the no observed or lowest observed effect level from an animal study. Uncertainty factors are then applied. These are interspecies extrapolation (animal to man), intraspecies sensitivity (hypersusceptible individuals/populations), and a modification for time and route of application. In more sophisticated assessment by the inhalation route, physiological considerations are often used to calculate the equivalent human systemic dose at an animal no effect concentration. These principles are discussed below. lnterspecies Extrapolation. The default uncertainty factor of 10 for animal-to-man extrapolation, based on sensitivity to the toxic end point, need not be applied because studies show that human beings are not more sensitive than rats, the species for which the no effect level was determined. Theoretically, an uncertainty factor of 0.1 could be applied in recognition of the fact that human red cells are at least 1 0 time less sensitive to haemolysis than those from rats. Intraspecies Sensitivity. The usual uncertainty factor of 10 for human variation (susceptible populations) need not be applied. Udden (1994) showed that RBCs from populations with certain haemolytic diseases were no more susceptible to 2-butoxyacetic acid-induced haemolysis than blood cells from healthy young humans. Modification for time and route of exposure. Some regulatory authorities apply an additional uncertainty factor for subchronic to chronic exposure if the human exposure potential is for a significant portion of the life-span, as for example in long- term occupational exposure. The question to be addressed i

L24 ANSWER 13 OF 41 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 94:736209 SCISEARCH
THE GENUINE ARTICLE: PR790
TITLE: MACROPHAGES LOADED WITH DOXORUBICIN BY ATP-MEDIATED PERMEABILIZATION - POTENTIAL CARRIERS FOR ANTITUMOR THERAPY
AUTHOR: MUNERATI M; CORTESI R; FERRARI D; DIVIRGILIO F (Reprint); NASTRUZZI C
CORPORATE SOURCE: UNIV FERRARA, INST GEN PATHOL, VIA BORSARI 46, I-44100 FERRARA, ITALY (Reprint); UNIV FERRARA, INST GEN PATHOL, I-44100 FERRARA, ITALY; UNIV FERRARA, DEPT PHARMACEUT SCI, FERRARA, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH, (10 NOV 1994) Vol. 1224, No. 2, pp. 269-276.
ISSN: 0167-4889.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 37
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In many cell types extracellular ATP (ATP(e)) has been shown to cause **reversible** plasma membrane permeabilization to low molecular weight (< 900 Da) water-soluble compounds. In the present report we have exploited this technique to incorporate the anticancer drug doxorubicin (DXR), molecular mass 543 Da, into the cytoplasm of two mouse cell lines that had previously been shown to express the ATP(e)-gated pore, J774 macrophages and tumor necrosis factor (TNF)-resistant L929 fibroblasts. Compared to passively loaded cells, ATP(e)-mediated **reversible** permeabilization allowed an at least Lt-fold increase in DXR intracellular trapping (0.5 pg/cell versus 2 pg/cell). Analysis of the release kinetics at 37 degrees C showed that about 40% of total intracellular DXR was discharged during the first hour from both ATP(e)-permeabilized and passively loaded cells; about 15% further release was observed upon **incubation** up to 4 h. DXR release profiles were similar in ATP(e)-permeabilized and passively loaded cells. ATP(e)-permeabilized, DXR-loaded (ATP(e)-DXR) cells strongly inhibited the proliferation of K562 tumor cells. Taken together these results indicate that ATP(e)-mediated **reversible** plasma membrane permeabilization can be effectively used to load cells of different histotypes with high concentrations of DXR. This approach could permit to vehicle high doses of anticancer agents by using living cells while reducing systemic **toxic effects**.

L24 ANSWER 14 OF 41 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 93129209 MEDLINE
DOCUMENT NUMBER: 93129209 PubMed ID: 1336367
TITLE: Cysteine protects Na,K-ATPase and isolated human lymphocytes from silver toxicity.
AUTHOR: Hussain S; Anner R M; Anner B M
CORPORATE SOURCE: Laboratory of Experimental Therapeutics, Geneva University Medical Center, Switzerland.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1992 Dec 30) 189 (3) 1444-9.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930226
Last Updated on STN: 20000303
Entered Medline: 19930208

AB Metal-binding proteins are important components of retroviruses such as human immunodeficiency virus (HIV). Therefore, metals could be used as antiviral agents. However, most metals are **toxic** for humans with the exception of silver which is **toxic** only to prokaryotic cells and viruses. In addition, HIV infection causes a decrease in body cysteine. We formed a complex of silver and cysteine, named silver-cysteine. Healthy human **lymphocytes** were **incubated** with silver-nitrate or silver-cysteine. Negligible cell survival was seen at 50 microM silver-nitrate. However, in presence of 1 mM cysteine, the viability remained unaffected up to 1 mM of silver. Further, silver inhibition of isolated Na,K-ATPase was easily **reversed** by cysteine. Thus, non-**toxic** silver-cysteine could be used as an anti-viral and cysteine-replenishing agent.

L24 ANSWER 15 OF 41 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 92227951 MEDLINE
DOCUMENT NUMBER: 92227951 PubMed ID: 1565099
TITLE: A sodium channel opener inhibits stimulation of human peripheral blood mononuclear cells.
AUTHOR: Pieri C; Recchioni R; Moroni F; Marcheselli F; Falasca M; Krasznai Z; Gaspar R; Matyus L; Damjanovich S
CORPORATE SOURCE: Cytology Center, Gerontological Research Department, I.N.R.C.A., Ancona, Italy.
SOURCE: MOLECULAR IMMUNOLOGY, (1992 Apr) 29 (4) 517-24. Journal code: 7905289. ISSN: 0161-5890.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 19920607
Last Updated on STN: 19920607
Entered Medline: 19920520

AB The role of membrane potential changes in T cell activation was studied on human peripheral blood **lymphocytes** stimulated with phytohemagglutinin. Addition of bretylium tosylate, a sodium channels opener, to PHA treated **lymphocytes** modified the membrane potential and consequently blocked cell activation in a dose-dependent fashion. BT was non-**toxic** even in long-term (72 hr) **incubations**. It was **reversibly** removable, and the removal restored the stimulatory effect of PHA. 3H-thymidine incorporation was blocked if BT was present during the first 20-24 hr of the mitogenic activation. The later BT was added after PHA, the less inhibition of proliferation was observed. BT hyperpolarized the **lymphocytes** also in the presence of PHA. BT hindered the depolarizing effect of high extracellular potassium concns. The sustained polarized state of the **lymphocytes** did not influence the intracellular calcium increase upon PHA treatment. IL-2 and transferrin receptor expression was not hindered by BT during PHA stimulation of **lymphocytes**. Addition of rIL-2 did not abolish the inhibitory effect of BT. According to cell-cycle analysis BT arrested the majority of the cells in G1 phase. It is suggested that cell activation demands the flexible maintenance of a relatively narrow membrane potential "window". Any sustained and significant hyper-, or depolarization, may dramatically decrease the effectivity of transmembrane signalling.

L24 ANSWER 16 OF 41 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 93052514 MEDLINE
DOCUMENT NUMBER: 93052514 PubMed ID: 1330897
TITLE: Interleukin-2 may enhance or inhibit antibody production by B cells depending on intracellular cAMP concentrations.
AUTHOR: Dennig D; Mecheri S; Bourhis J H; Hoffman M K
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
CONTRACT NUMBER: AI:AC 26067 (NIAID)
SOURCE: IMMUNOLOGY, (1992 Oct) 77 (2) 251-5. Journal code: 0374672. ISSN: 0019-2805.

PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921223

AB The primary IgM response of murine B **lymphocytes** against red blood cell-bound antigens can be induced by **incubating** antigen-reactive B cells either with the lymphokines interleukin-1 (IL-1) and IL-2 together with the nucleoside cAMP, or by the addition of antigen-specific helper T cells. The reactivity of B cells is strongly influenced by the T-cell lymphokine IL-2. IL-2 inhibits the cyclic adenosine 3',5'-phosphate (cAMP)-dependent B-cell response when it is allowed to act on the cells prior to cAMP. On the other hand, if IL-2 acts on B cells together with or after cAMP, it synergizes with the nucleoside and enhances the immune response. A similar effect of IL-2 is observed in the T-cell-mediated activation of B cells. If IL-2 is present before helper T cells interacted with B cells, it inhibits antibody production. The inhibitory IL-2 effect is **reversed** by the simultaneous addition of exogenous cAMP. The finding supports the hypothesis that Ia ligation by T cells results in B cells in the elevation of cAMP which acts as an important second messenger in B cells. The antagonism between cAMP and IL-2 was also examined in the pre-B-cell line 70Z/3. The nucleoside is highly **toxic** to 70Z/3 pre-B cells and a majority disintegrates within hours of exposure to the nucleoside. The surviving cells undergo phenotypic differentiation expressing surface Ig kappa chains and major histocompatibility complex (MHC) class II molecules, and increase the expression of IL-2 receptor (R). The phenotypic differentiation requires the presence of IL-1. IL-2 inhibits both of these B-cell responses to cAMP, the IL-1-independent cell death, and the IL-1-dependent phenotypic differentiation.

L24 ANSWER 17 OF 41 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:431388 TOXCENTER
DOCUMENT NUMBER: EMIC-86958
TITLE: STUDIES ON THE **REVERSAL** OF AZIDOTHYMIDINE **TOXICITY** IN HUMAN LYMPHOCYTES BY CYTIDINE AND URIDINE.
AUTHOR(S): COX S
CORPORATE SOURCE: DEPARTMENT OF VIROLOGY, NATIONAL BACTERIOLOGICAL LABORATORY AND DEPARTMENT OF VIROLOGY, KAROLINSKA INSTITUTE, STOCKHOLM, SWEDEN.
SOURCE: Antiviral Chemistry & Chemotherapy, (1991) 2 (1) 23-8.
CODEN: ACCHE. ISSN: 0956-3202.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: EMIC
OTHER SOURCE: EMIC MUT-92000592
LANGUAGE: English
ENTRY DATE: Entered STN: 20021200
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AB THE **TOXICITY** OF 3'-AZIDOTHYMIDINE (AZT) IN HUMAN **LYMPHOCYTES** HAS BEEN SHOWN PREVIOUSLY TO BE **REVERSED** BY CO-**INCUBATION** WITH THE RIBONUCLEOSIDES CYTIDINE OR

URIDINE. IN THE PRESENT PAPER, THE EFFECTS OF 3'-AZIDOTHYMIDINE AND CYTIDINE/URIDINE, BOTH ALONE AND IN COMBINATION, WERE STUDIED UPON KEY PROCESSES IN LYMPHOCYTES IN ORDER TO DISCOVER MORE ABOUT THE MECHANISM OF **TOXICITY REVERSAL**. IN THESE EXPERIMENTS 3'-AZIDOTHYMIDINE HAD ONLY MINOR EFFECTS ON THE RIBONUCLEOSIDE TRIPHOSPHATE POOLS. CYTIDINE INCREASED THE CTP POOL, AND URIDINE THE UTP POOL. CO-INCUBATION WITH AZT CAUSED SIMILAR CHANGES TO INCUBATION WITH CYTIDINE OR URIDINE ALONE. **TOXICITY REVERSAL** WAS NOT LINKED TO REPLACEMENT OF DEFICIENT RIBONUCLEOSIDE TRIPHOSPHATE POOLS. 3'-AZIDOTHYMIDINE CAUSED THE EXCRETION OF THYMIDINE FROM LYMPHOCYTES. INCUBATION WITH CYTIDINE AND URIDINE INCREASED THE INTRACELLULAR CYTIDINE AND URIDINE POOLS, RESPECTIVELY. CO-INCUBATION WITH 3'-AZIDOTHYMIDINE INCREASED STILL FURTHER THE INTRACELLULAR CYTIDINE AND URIDINE POOLS. CYTIDINE AND URIDINE DID NOT AFFECT THE INTRACELLULAR 3'-AZIDOTHYMIDINE POOL. THE TOXICITY OF 3'-AZIDOTHYMIDINE WAS INCREASED BY CO-INCUBATION WITH THE BASES ADENINE, GUANINE, HYPOXANTHINE, AND URACIL, BUT NOT BY DIHYDROURACIL, THYMINE, OR XANTHINE.

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L24 ANSWER 19 OF 41 MEDLINE DUPLICATE 10
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AUTHOR: Berenson C S; Ryan J L
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AB Gangliosides have been shown to act as immunoregulatory agents by altering proliferative responses of **lymphocytes** to both antigens and mitogens. Most early studies have utilized brain gangliosides and have required high concentrations. The role of endogenous gangliosides from macrophages has remained unexplored. In this study, thioglycolate-elicited murine peritoneal macrophage gangliosides were purified and added to cultures of murine **lymphocytes**. Nanogram amounts caused a profound inhibition